# Response to the NICE Appraisal Consultation Document

# Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years

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# PART A CLINICAL RESPONSE

## *1. Background*

BMS/OPUK present below an outline of the additional requests from NICE regarding the clinical information of aripiprazole and the relevant comparators.

## *2. Clinical information requested*

The Committee requested additional evidence relating to the clinical effectiveness of aripiprazole compared with: risperidone; olanzapine; quetiapine; amisulpride and clozapine, and the examination of the relative effectiveness of each agent compared with placebo and each other. Outcomes should include: PANSS; PANSS subscales; CGI-severity; CGI-improvement; CGAS; P-QLES-Q.

In addition, information about how the clinical effectiveness of aripiprazole may differ for people ages 15-17 years with schizophrenia, who also have learning difficulties, is required.

### 2.1 Clinical response: data sources

[redacted]

Information from placebo controlled trials in adolescent schizophrenia is provided for risperidone, olanzapine and quetiapine (see Appendix A). There are no placebo controlled randomised clinical trial data for amisulpride, neither are there placebo controlled data for clozapine. Not all the placebo controlled studies provide all the clinical endpoints requested, so data have been extracted and presented where available (see Appendices B and C). In 3 studies the primary measure was measured in outcomes other than PANSS (i.e. as BPRS and SANS).

The source for much of these data have been taken from the recent review by Fraguas et al (2010) which provided a comprehensive review of prospective head-to-head and placebo-controlled comparisons of the efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders.

Fraguas et al indicate that there were 3 clozapine studies (on small numbers of patients) which suggested clozapine had superior efficacy in refractory schizophrenia – these have not been included, due to the small numbers of patients, and also because refractory schizophrenia is outside the scope of this appraisal.

Recent data on risperidone (Haas et al 2009a) has also been included. This paper was not included in the original submission's systematic review as it was published after the cut-off period for the search. Following the Committee's request we carried out a second search for risperidone data in the adolescent population and included this evidence.

Data on quetiapine in a placebo controlled adolescent schizophrenia study has been taken from Findling et al (2008b), which is a poster presented at the AACAP (2008), and so would not have been included in the Fraguas et al review paper.

The level of analysis requested, the lack of suitable data and the lack of time afforded in the timeline have meant BMS/ OPUK needed to take a pragmatic approach. A complete indirect comparison of all the requested end points has not been conducted. However, BMS/OPUK have updated the existing indirect comparison used for the economic model. Additional endpoints have been presented as a clinical summary only. BMS/OPUK feel this is a reasonable compromise between what is achievable in the time available, which can be referenced to a comprehensive, published independent review covering the majority of data requested.

- **Data sources include a recent, comprehensive, independent review of second generation antipsychotics in adolescents.**
- **This was felt to be the best compromise outwith a full, new, systematic review and meta-analysis, due to the limited time available for this response.**
- **The review also has the benefit of being fully independent of BMS/ OPUK.**

## 2.2 Response: efficacy

Fraguas et al (2010) concluded that there were no significant differences between second generation antipsychotics in terms of short term efficacy. BMS/ OPUK feel that the overall position stated by Fraguas et al is correct, as can be seen from the data extracted from the source publications from placebo-controlled trials (Appendix B).

Regarding long term efficacy, there is an additional 26 week open label extension study available for aripiprazole in adolescent patients that was conducted in patients between 13 to 17 years of age. Correll et al (2009a) presented a sub-analysis of adolescent patients between the ages of 15 to 17 years. Here, 80.2% of adolescents achieved response to treatment at week 32 (OC dataset).

These long-term data for aripiprazole in adolescents was part of the submission to the CHMP and do not exist for any other antipsychotic. Based on the long term data provided, and an additional post-hoc analyses, the CHMP concluded that maintenance of effect was observed with aripiprazole in adolescents with schizophrenia aged 15 to 17 (Abilify SmPC).

Within the framework of a recent harmonisation of risperidone's SmPC in the European Union, the CHMP reviewed all the available evidence in adolescents with schizophrenia and concluded that risperidone should not be recommended for use in children with schizophrenia below 18 years of age due to lack of data on efficacy.

- **Based on the available data from placebo-controlled, randomised clinical trials in adolescent schizophrenia, there are no significant differences in short term efficacy between the second generation antipsychotics aripiprazole, risperidone, olanzapine, quetiapine, amisulpride and clozapine.**
- **Based on a sub-analysis that was submitted to the CHMP, aripiprazole maintenance of effect was observed over a 26 week open label extension trial.**

## 2.3 Response: safety

Fraguas el al (2010) concluded that there were differences among second generation antipsychotics in terms of safety. Mean weight gain varied by drug (Table 1)

**Table 1 Mean weight gain by antipsychotic (all studies) (from Fraguas et al 2010)**

| Second generation antipsychotic | Mean weight gain range (Kg) |
|---|---|
| Olanzapine | 3.8—16.2 |
| Clozapine | 0.9—9.5 |
| Risperidone | 1.9—7.2 |
| Quetiapine | 2.3—6.1 |
| Aripiprazole | 0—4.4 |

[redacted] These data agree with the findings from Fraguas et al (2010).

Correll et al (2009b) and De Hert et al (2010) also compared other lipid and metabolic parameters. These data indicated that while aripiprazole was not associated with any significantly worsened metabolic indices (Appendix C), [redacted]

Weight gain and lipid/glucose abnormalities during development are amongst the risk factors that predict adult obesity and metabolic/ cardiovascular morbidity (Srinivasan et al 2002; Sinaiko et al 1999; Bhargava et al 2004; Baker et al 2007).

[redacted]

In their review, Fraguas el al (2010) concluded that prolactin levels increased most in patients receiving risperidone (mean change from 8.3 to 49.6 ng/mL) followed by olanzapine (–1.5 to +13.7 ng/mL). However, there was no evidence of hyperprolactinaemia with aripiprazole in adolescent patients. Based on data from adult and child studies (Correll 2006) the relative potency of a range of antipsychotic drugs including aripiprazole, olanzapine, quetiapine, risperidone and clozapine show that aripiprazole has the lowest risk of inducing hyperprolactinemia. Finally, in an observational study in youths (4-19 years) treated with atypical antipsychotics for

psychotic, mood and aggressive spectrum disorders Correll (2007) found that hyperprolactinemia (>25.7 ng/mL) was present in 84.1% of youngsters on risperidone, 52.9%, on olanzapine, 14.4% on quetiapine, and 9.5% on aripiprazole ($p<0.0001$).

Elevated serum prolactin levels have been shown to have effects on sexual function, menstrual function as well as being associated with decreased bone mineral density in women (Hanssens et al 2008; Mah et al, 2002; Klibianski et al, 1980). Sexual dysfunction is a much under-reported side-effect of antipsychotics, which has also been closely linked with non-compliance to the anti-psychotic treatment regimen (Smith et al 2002; Fleischacker et al 1994). Hypothetically, these effects may be more pronounced in adolescents than in adults due to age-related decreases in dopamine receptors (Correll et al, 2006), but there are no firm data in this regard.

With respect to neuromotor symptoms (i.e. EPS, which includes akathisia) most studies found no significant differences between the second generation antipsychotics.

Overall Fraguas et al considered that the heterogeneity displayed by the second generation antipsychotics was mainly due to differences in the rate and severity of side effects, especially regarding weight gain (as a proxy for the risk of cardiovascular events) and prolactin levels. BMS/ OPUK believe that the position stated by Fraguas and colleagues is correct, as can be seen from the data extracted from the source publications from placebo-controlled trials (Appendix C).

- **Based on the available data from placebo-controlled, randomised clinical trials in adolescent schizophrenia, there are important differences in side effects between the second generation antipsychotics and aripiprazole comes out favourably in this respect.**
- **In contrast to other agents, aripiprazole is not associated with any significant increases in weight or prolactin levels.**

## 2.4 Response: learning difficulties

There is a paucity of data in this area. Aripiprazole did demonstrate a significant improvement in the Children's Global Assessment Scale compared with placebo (Findling et al 2008a), which would suggest an improvement in overall global

functioning in adolescent patients with a diagnosis of schizophrenia. However BMS/ OPUK do not have any direct data addressing the effects of aripiprazole in patients with learning difficulties, other than that which was addressed in previous submissions and responses.

The primary use of aripiprazole is to treat the psychoses associated with schizophrenia. The diagnosis of schizophrenia requires a definitive methodological approach using precise DSM-IV and K-SADS-PL criteria, so patients are diagnosed as either suffering, or not suffering, from schizophrenia using these diagnostic tools.

Some individuals with learning difficulties may exhibit psychoses, some may not. If, based on their psychoses, they are classified as schizophrenic, aripiprazole may be appropriately prescribed in order to treat their psychoses. BMS/ OPUK do not have any further information in this regard.

- **There is a paucity of clinical data available regarding the use of aripirazole in adolescents with schizophrenia, who also have learning difficulties.**

## *3. Comment on clinical specialists' feedback (from consultation document)*

As presented in the NICE appraisal consultation document, clinical specialists recognise that no single atypical antipsychotic drug is considered to be more clinically effective than others. This position is also supported by Fraguas et al (2010). However, aripiprazole is the only licensed option for the treatment of adolescent schizophrenia with a low risk of some of the most common, problematic, adverse events associated with atypical use - namely weight gain, akathisia and abnormal prolactin levels (which can be considered a proxy for sexual dysfunction).

- **Aripiprazole is associated with a better efficacy/safety profile compared with other second generation anti-psychotics used in adolescents.**

## 3.1 Aggression.

The Committee mentioned aggression specifically. Aggression is a difficult item to assess: for example, because aripiprazole has less sedative effects than other second generation agents, less somnolence and more awareness might manifest itself as a patient seeming more "aggressive" compared to their usual state. However, the *ad hoc* comment at the Appraisal Committee aside, "aggression" is not reported or recognised as an issue in the literature nor in the current ABILIFY SmPC. For example, Findling et al (2008a) cite a number of different adverse events as occurring in ≥5% of patients in any group. They include agitation (placebo: 5%; aripiprazole 10mg: 1%; aripiprazole 30mg: 3%) but not aggression *per se*. Indeed, a recent paper by Robb et al (2010) reports a reduction on the PANSS hostility factor with aripiprazole in adolescents, which is not suggestive of any increase in aggression. Two 8-week randomised placebo controlled multicentre studies have been carried out in children and adolescents with autistic spectrum disorder (Marcus et al 2009; Owen et al 2009). Aripiprazole was effective in reducing irritability and aggression in this population. Finally, Fraguas et al (2010) do not specifically mention aggression in their review. BMS/ OPUK therefore consider that aggression is not perceived to be an issue with aripiprazole, or indeed any other second generation agent.

**Aggression does not seem to be a recognised issue for aripiprazole treated patients.**

## 3.2 Clozapine

The clinical specialists also highlighted the unique position of clozapine (i.e. reserved for use in refractory schizophrenia). With regards to assessing efficacy, the PANSS scale was used for aripiprazole, risperidone, olanzapine and quetiapine, but not for clozapine – thus reinforcing the uniqueness of clozapine's position opposite the other atypicals.

Additionally, the SPC for clozapine shows that the agent is only indicated for treatment resistant schizophrenia, and should not be used in patients under 16 years of age.

BMS/ OPUK therefore do not consider it appropriate to compare aripiprazole's clinical effectiveness and safety profile with clozapine: rather clozapine will be

considered more fully in the economic section with regard to its position as “rescue medication”.

**Clozapine’s unique position as the antipsychotic of choice for treatment resistant schizophrenia precludes it from being usefully compared with regards to clinical effectiveness and safety against aripiprazole, or other second generation atypicals.**

### 3.3 Treatment options

Finally, the Committee agreed with the clinical specialists that it is important for adolescents to have a range of treatment options, and therefore concluded that aripiprazole may be a suitable option compared with risperidone, olanzapine, quetiapine or amisulparide for people aged 15 years or older with schizophrenia. BMS/ OPUK agree with this position. Denying patients and clinicians access to aripiprazole will limit patient and clinical choice, especially when considering that aripiprazole is the only second generation antipsychotic actually licensed for use in adolescents.

**Aripiprazole is the only licensed, commonly used atypical for the treatment of schizophrenia in people aged 15-17 years of age. Denying access to aripiprazole would limit patient and clinician choice.**

## *4. Summary*

- Olanzapine, quetiapine and risperidone are not licensed for use in England and Wales in people aged 15-17 years old.
- Amisulpride, although licensed for use in adolescents, is infrequently prescribed due to its effect on prolactin levels
- Clozapine is prescribed only when patients are refractory to initial antipsychotic treatment
- Aripiprazole is the only commonly used second generation antipsychotic licensed for adolescents
- Aripiprazole has the most favourable efficacy/safety profile of the second generation antipsychotics used in adolescents in England and Wales.

## References


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# Part B ECONOMIC RESPONSE

## *5. Introduction*

BMS/ OPUK present below an outline of the additional requests from NICE regarding the cost-effectiveness of aripiprazole and how these have been addressed.

The requests are outlined below:

**ACD Section 1.5**

Include an economic analysis of aripiprazole incorporating the following comparators: risperidone; olanzapine; quetiapine; and clozapine (as rescue treatment). An analysis is required for the following four treatment sequences:

- aripiprazole followed by risperidone then olanzapine then clozapine
- risperidone followed by aripiprazole then olanzapine then clozapine
- risperidone followed by olanzapine then aripiprazole then clozapine
- risperidone followed by olanzapine then quetiapine then clozapine.

**ACD Section 1.6**

For each of the four treatment sequences outlined above the following factors should be considered:

- A range of doses for each comparator, including low doses (which are commonly prescribed for adolescents)
- Observed differences (and standard errors) in PANSS scores
- The sensitivity of the incremental cost-effectiveness ratio (ICER) to rates of relapse informed by PANSS scores
- Data on all adverse treatment effects, including; weight gain, extrapyramidal symptoms such as akathisia, sexual dysfunction (modelled if necessary from the incidence of hyperprolactinaemia), somnolence, and aggression
- Inclusion of lay utility values (rather than patient values) from Briggs et al.

## 5.1 Methods

The following steps have been taken to address the requests made by NICE:

- Identify additional data required

- Data were extracted from the two additional studies identified and indirect comparisons on relevant outcomes were performed
- The original economic model was adapted to include a fourth treatment line and additional adverse events. Lay utility values from Briggs et al. were incorporated and a range of doses for each comparator, including low doses (which are commonly prescribed for adolescents) were explored. In addition, inaccuracies identified by the ERG in the original model were also corrected
- Base case results and sensitivity analyses were re-run using the adapted model.

# *6 Additional data identified*

## 6.1 Outcomes

Additional sources of effectiveness data for risperidone and quetiapine were identified and added to the model to address the request in the ACD (sections 1.5 and 1.6).

A brief updated literature search was conducted (including conference proceedings which were not previously searched) to identify additional data for risperidone and quetiapine. Two additional adolescent data sources were identified; one for quetiapine from conference proceedings (Findling et al. 2008) and one for risperidone via OVID (Haas et al. 2009). Both studies were placebo controlled trials of atypical antipsychotics (risperidone and quetiapine) conducted in adolescents with schizophrenia.

**Risperidone**

Haas et al 2009 A 6-Week, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Risperidone in Adolescents with Schizophrenia. Journal of child and adolescent psychopharmacology. Volume 19, Number 6, pp 611–621

**Quetiapine**

Findling et al 2008 Efficacy and safety of quetiapine in adolescents with schizophrenia: a 6-week, double-blind, randomized, placebo-controlled trial. Abstract presented at the 55th Annual Meeting of the American Academy of Child & Adolescent Psychiatry, October 28-November 2, 2008, Chicago, Illinois, USA

The olanzapine study (Kryzhanovskaya et al. 2009) was also re-reviewed to determine if any additional adverse events outlined in section 1.6 of the ACD could be incorporated into the model.

Data were extracted from the identified studies and results for efficacy (withdrawals) and adverse events (weight gain, somnolence, akathisia, tremor, received benzodiazepines and agitation) were used to inform indirect comparisons of risperidone and quetiapine with aripiprazole. Data were also extracted on different doses (where available) to inform the sensitivity analysis requested in section 1.6 of the ACD.

From the data extraction of Findling et al. 2008 (quetiapine) and Haas et al. 2009 (risperidone) and re-extraction of Findling et al. 2008 (aripiprazole) additional outcomes were identified (Table 2). None of these additional outcomes were identified in the olanzapine trial (Kryzhanovskaya et al. 2009).

**Table 2: Additional outcomes identified versus original outcomes included**

| Outcomes in the original submission | Additional outcomes identified |
|---|---|
| Withdrawals due to adverse events (AEs) | Akathisia |
| Withdrawals due to lack of efficacy | Tremor |
| Withdrawals due to other reasons | Agitation |
| Weight gain >=7% | |
| Somnolence | |
| Received benzodiazepines | |

The data extracted from the identified studies is provided in Appendix D. Additional indirect comparisons for aripiprazole versus risperidone and quetiapine were carried out using these data. Data were not available for all comparators for all outcomes. The odds ratios (ORs) resulting from the indirect comparison analyses are presented in Table 3 which also identifies where data were not reported for each of the outcomes for each treatment (N/A).

**Table 3 Odds ratios from the indirect comparisons – aripiprazole compared with olanzapine, risperidone and quetiapine**

| Outcome | Olanzapine FD* | Risperidone 1-3mg | Risperidone 4-6mg | Quetiapine 400mg | Quetiapine 800mg |
|---|---|---|---|---|---|
| Withdrawals due to adverse events (AEs) | 1.57 (0.06 to 43.88) | 0.41 (0.04 to 4.61) | 0.60 (0.06 to 6.38) | 0.73 (0.07 to 7.35) | 1.03 (0.11 to 9.96) |
| Withdrawals due to lack of efficacy (LoE) | 0.03 (0.00 to 0.31) | 0.03 (0.00 to 0.44) | 0.01 (0.00 to 0.24) | N/A ** | N/A ** |
| Withdrawals due to other reasons | 3.73 (0.48 to 28.70) | 4.92 (0.53 to 45.41) | 2.56 (0.23 to 29.07) | 0.67 (0.15 to 2.95) | 0.30 (0.06 to 1.47) |
| Weight gain >=7% | 0.51 (0.02 to 11.50) | N/A | N/A | 0.41 (0.02 to 9.34) | 0.30 (0.01 to 6.92) |
| Somnolence | 5.34 (0.54 to 53.01) | 4.16 (0.65 to 26.67) | 1.79 (0.26 to 12.56) | 2.73 (0.63 to 11.87) | 3.06 (0.71 to 13.23) |
| Akathisia | N/A | N/A | N/A | 1.56 (0.17 to 14.40) | 1.54 (0.17 to 14.19) |
| Tremor | N/A | 2.08 (0.18 to 24.08) | 1.85 (0.16 to 21.96) | 1.56 (0.11 to 23.01) | 1.54 (0.10 to 22.69) |
| Received benzodiazepines | 0.39 (0.14 to 1.08) | N/A | N/A | 0.96 (0.37 to 2.50) | 0.63 (0.23 to 1.69) |
| Agitation | N/A | 11.09 (0.90 to 136.10) | 5.54 (0.41 to 74.75) | 3.03 (0.27 to 33.92) | 2.99 (0.27 to 33.42) |

*olanzapine results are shown as in the original submission. NA – data not available for this comparison
**the OR of withdrawal due to LoE is assumed to be captured in withdrawal due to other reasons. Therefore the OR in the model is set to zero. For all other missing ORs equivalence to aripiprazole was assumed (i.e. the OR was set to 1).

The ORs shown in Table 3 include the results for olanzapine compared with aripiprazole from the original submission. No additional data from the olanzapine trial (Kryzhanovskaya et al. 2009) were available to inform indirect comparisons versus aripiprazole for akathisia, tremor and agitation.

Although every effort was made to identify and compare rates of sexual dysfunction and aggression, these were not available from the clinical trial data in a format appropriate to inform the economic model.

## Sexual dysfunction

The incidence of sexual dysfunction was not provided in the clinical trials identified. No questionnaires regarding sexual dysfunction appeared to have been used in any of the trials identified. Prolactin levels, which are thought to be linked to sexual dysfunction, were reported in different ways in each of the trials. For example, Findling et al. 2008 (the aripiprazole trial) describes a percentage of patients with low prolactin levels, whereas Kryzhanovskaya et al. 2009 (the olanzapine trial) describes the number of patients with treatment emergent high prolactin levels. Haas 2009 reported mean change in prolactin levels. We were therefore unable to include the rates of sexual dysfunction in the model with any degree of appropriateness or consistency between the treatments. Any attempt to do so would introduce immeasurable bias into the model.

## Aggression

Data on aggression were not consistently reported in the identified studies. Data on psychiatric disorders including aggression were collected in the aripiprazole clinical trial (CSR). However, none of the other studies identified reported incidence of aggression. Kryzhanovskaya et al. 2009 describes the mean change from baseline in OAS (overt aggression scale) but does not report incidence, or data in a comparable format to aripiprazole. No data were reported on aggression in either Haas et al. 2009 (risperidone trial) or Findling et al. 2008 (quetiapine trial). To attempt to address this issue, rates of agitation (available for aripiprazole, risperidone and quetiapine) were included as a sensitivity analysis. However, it is unknown if agitation would be an appropriate proxy for aggression as it is more likely to be reported as a symptom of EPS.

## Clozapine

When conducting research for the original model structure submitted, clozapine was considered a rescue therapy and was not considered an appropriate comparator for aripiprazole in the adolescent population. For this reason, clozapine was only included in the model as a marker for rescue treatment. No clinical data on its use in the adolescent population was identified. As clozapine is considered to be a rescue treatment, meaning that no further treatment would be available, we assumed that there would be no discontinuation once on clozapine, but patients accumulate costs associated with clozapine treatment and the monitoring that is required. The costs and utilities associated with adverse events while on clozapine may also be included as a sensitivity analysis where they are assumed to be the same as those experienced by patients on aripiprazole.

## PANSS

During the development of the original model, a literature review was conducted of previous cost effectiveness studies to inform the model methods. In conjunction with this review, clinicians were consulted to understand the outcome measures that were viewed as the most appropriate, and commonly used in clinical practice, to establish response in adolescents receiving therapies for schizophrenia. It was identified that clinicians do not routinely use the PANSS questionnaire to establish response, and that relapse was considered an important outcome measure. This was also highlighted during the committee meeting when the following observation was noted:

"*The Committee heard from the clinical specialists that the PANSS score (primary outcome) is a well-recognised tool used in clinical trials, however the results are often difficult to relate to UK clinical practice as the tool is not routinely used by clinicians."*

In order to keep the model representative of clinical practice, PANSS was therefore not included.

During the review of the literature consideration of other cost effectiveness analyses conducted in this area were used as a guide to include or exclude PANSS in the model. In particular we reviewed in detail the economic evaluation conducted by NICE as part of the clinical guideline CG82. This model structure was used to inform the original model structure used in the STA submission. The NICE model took PANSS into consideration when identifying and informing utility values rather than as a separate outcome measure. However, more recent data on utility values in adults with schizophrenia has concluded that the PANSS score did not influence the utility results independently of health state (Briggs et al 2008). Therefore, the model does

not include PANSS as an outcome measure. Although this is a noted limitation of the model, it is more reflective of clinical practice and the model outcomes are appropriate. Therefore as PANSS scores were not used in the model it was not possible to address the requests outlined below:

- Observed differences (and standard errors) in PANSS scores
- The sensitivity of the incremental cost-effectiveness ratio (ICER) to rates of relapse informed by PANSS scores.

## *7. Model alterations*

To address the requests outlined in the ACD section 1.6, and to address some of the previous feedback from the ERG, the original model submitted was adapted. The following changes were made:

- Data on risperidone and quetiapine have been added (withdrawal and adverse events at each dose available). Additional data on adverse events as a result has also been added to the model (akathisia, tremor and agitation)
- The ability to examine a fourth treatment line has been added
- The correct cost for an acute hospital stay (cost of relapse error highlighted by the ERG in their report) has been added, i.e. acute hospital stay = £513 per day (national average unit cost of 23,595/46 days) using NHS reference costs (HRG code PA52C, mapped from ICD10 code F200)
- The error in the costs during the second cycle of the model has been corrected – this has mainly been addressed by slightly restructuring the decision tree/Markov model following the ERG criticism of the flow of the model, which also made it more intuitive when adding the fourth treatment
- The correct relative risk of relapse from Moellar et al 2006 has been determined through correspondence with the authors and added to the model (unadjusted RR = 19.4/20.7 = 0.937)
- The model has been updated with the utility values reported by the lay population from Briggs et al
- Values for proportion of patients who have an acute hospitalisation and the number of patients receiving olanzapine (following relapse) have been limited so as not to exceed 100%.

Other than the above changes, the model remains the same as the original model submitted. Additional assumptions made to inform data gaps in the outcome measures are as follows:

- Where data were not available for any of the outcome measures, equivalence to aripiprazole was assumed. For example, weight gain >=7% was not reported in the risperidone study, therefore the OR was set to 1, that is, the same as for aripiprazole
- For quetiapine, the OR of withdrawal due to lack of efficacy is assumed to be captured in withdrawal due to other reasons. Therefore the OR in the model was set to zero
- Similarly for outcomes for clozapine equivalence to aripiprazole was assumed
- In order to be pragmatic and due to the time restraints regarding this additional analysis, the costs and disutility associated with EPS have been applied to other adverse events included in the model (akathisia, benzodiazepine use, agitation and tremor). The PSA varies the utility value and costs associated with adverse events in order to address this assumption.

# *8.0 Results*

## 8.1 Base case

The base case results included all comparators and sequences requested in the ACD section 1.5. The adverse events included in the base case are weight gain, somnolence and EPS (akathisia and tremor represent symptoms of EPS) as requested in ACD section 1.6. Rates of sexual dysfunction and aggression were also requested in ACD section 1.6 but were not available from the clinical trial data identified and have therefore not been included in the base case. Data on agitation were identified and used to inform a sensitivity analysis on the effect on the model of including this additional adverse event. The base case uses the following doses reported in the identified trials; aripiprazole 10mg, olanzapine 12.5mg (average dose), risperidone 1-3mg (lowest dose available) and quetiapine 400mg (lowest dose available). The ORs (rather than the RRs) from the indirect comparison were used as these are the most appropriate inputs for economic modelling.

Section 1.5 of the ACD requests that an analysis is completed for four treatments sequences (labelled A, B, C and D here for convenience):

A. aripiprazole followed by risperidone then olanzapine then clozapine
B. risperidone followed by aripiprazole then olanzapine then clozapine
C. risperidone followed by olanzapine then aripiprazole then clozapine
D. risperidone followed by olanzapine then quetiapine then clozapine.

Total costs and QALYs for these four treatment sequences are outlined in Table 4. The sequence with the highest QALYs is Aripiprazole - Risperidone - Olanzapine – Clozapine. The lowest cost sequence is Risperidone - Olanzapine - Aripiprazole – Clozapine.

**Table 4: Total costs and QALYs for each of the requested scenarios**

| | Sequence | Total costs | Total QALYs |
|---|---|---|---|
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | £23,530 | 2.2974 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | £22,812 | 2.2918 |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | £22,714 | 2.2899 |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | £23,428 | 2.2818 |

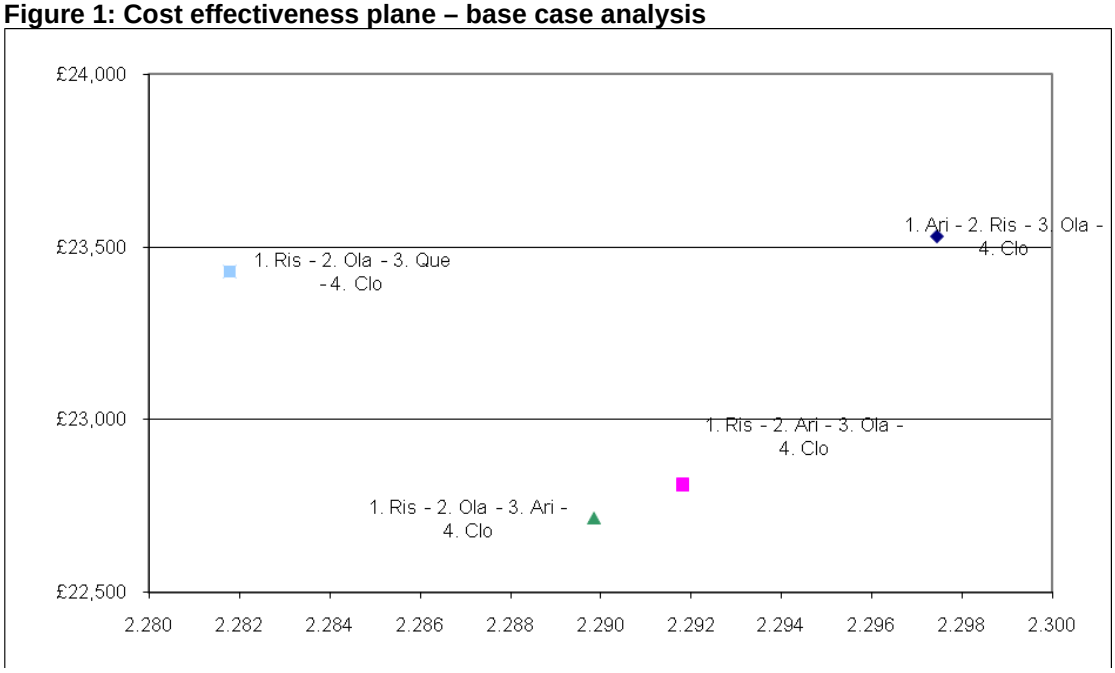
The ACD does not state which scenario should represent the base case, therefore all scenarios were compared with each other in the model and the cost per QALYs are provided in Table 5. If comparisons are made against the sequence that does not

contain aripiprazole, that is, sequence D, this sequence was found to be cost effective or dominant against all other sequences not containing aripiprazole. The cost effectiveness plane generated is shown in Figure 1.

**Table 5: Total costs and QALYs for each of the requested scenarios**

| | | A | B | C | D |
|---|---|---|---|---|---|
| | | 1. Ari - 2. Ris - 3. Ola - 4. Clo | 1. Ris - 2. Ari - 3. Ola - 4. Clo | 1. Ris - 2. Ola - 3. Ari - 4. Clo | 1. Ris - 2. Ola - 3. Que - 4. Clo |
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | - | £127,422 | £107,422 | £6,479 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | - | - | £49,893 | Dominant |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | - | - | - | Dominant |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | - | - | - | - |

**Figure 1: Cost effectiveness plane – base case analysis**



## 8.2 Deterministic sensitivity analyses

### Dosing sensitivity analysis

As requested in the ACD section 1.6, a sensitivity analysis was carried out on the doses used. Two scenarios were tested:

- Dosing Scenario 1: aripiprazole 10mg, olanzapine 12.5mg (as in the base case), risperidone 4-6mg and quetiapine 800mg (higher doses reported; both costs and efficacy were varied))
- Dosing scenario 2: aripiprazole 10mg, olanzapine 10mg (as tablets are available in 10mg doses; efficacy remains the same as in the base case), risperidone 4-6mg and quetiapine 800mg (both costs and efficacy varied).

### Dosing scenario 1

The results of this analysis are shown in Table 6 and Table 7. The overall direction of results does not change. The sequence with the highest QALYs is Aripiprazole - Risperidone - Olanzapine – Clozapine. The lowest cost sequence is Risperidone - Olanzapine - Aripiprazole – Clozapine. The cost effectiveness plane generated is shown in Figure 2

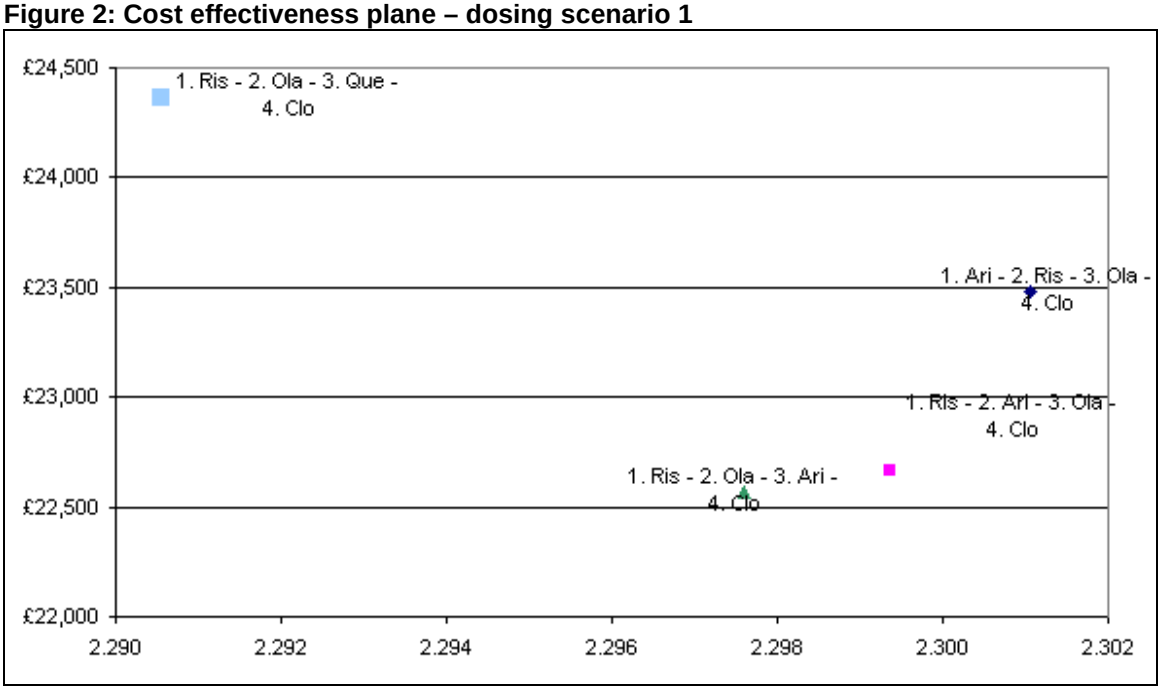
**Table 6: Total costs and total QALYs for dosing scenario 1**

| | Sequence | Total costs | Total QALYs |
|---|---|---|---|
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | £23,653 | 2.264 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | £22,982 | 2.246 |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | £22,884 | 2.244 |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | £23,607 | 2.233 |

**Table 7: ICERs for dosing scenario 1**

| | | **A** | **B** | **C** | **D** |
|---|---|---|---|---|---|
| | | 1. Ari - 2. Ris - 3. Ola - 4. Clo | 1. Ris - 2. Ari - 3. Ola - 4. Clo | 1. Ris - 2. Ola - 3. Ari - 4. Clo | 1. Ris - 2. Ola - 3. Que - 4. Clo |
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | - | £486,049 | £264,828 | Dominant |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | - | - | £53,555 | Dominant |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | - | - | - | Dominant |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | - | - | - | - |

**Figure 2: Cost effectiveness plane – dosing scenario 1**




## Dosing scenario 2

The results of this analysis are shown in Table 8 and Table 9. The overall direction of results does not change. The sequence with the highest QALYs is Aripiprazole - Risperidone - Olanzapine – Clozapine. The lowest cost sequence is Risperidone - Olanzapine - Aripiprazole – Clozapine. The cost effectiveness plane generated is shown in Figure 3.

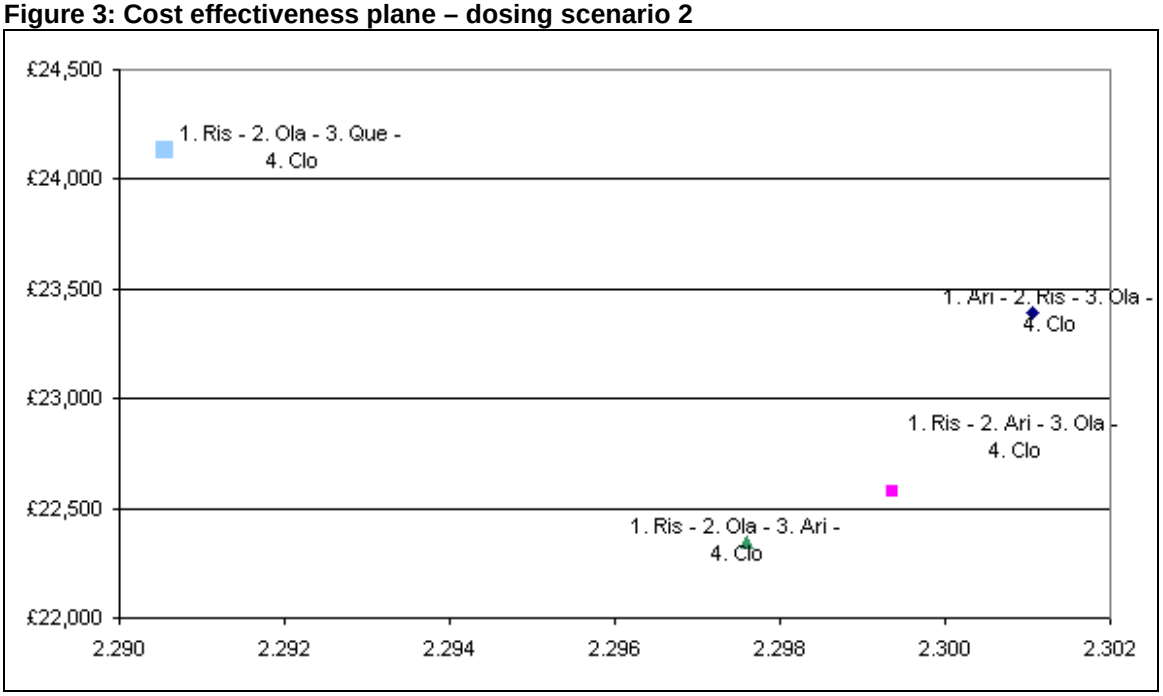
**Table 8: Total costs and total QALYs for dosing scenario 2**

| | Sequence | Total costs | Total QALYs |
|---|---|---|---|
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | £23,392 | 2.301 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | £22,574 | 2.299 |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | £22,341 | 2.298 |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | £24,138 | 2.291 |

**Table 9: ICERs for dosing scenario 2**

| | | **A** | **B** | **C** | **D** |
|---|---|---|---|---|---|
| | | 1. Ari - 2. Ris - 3. Ola - 4. Clo | 1. Ris - 2. Ari - 3. Ola - 4. Clo | 1. Ris - 2. Ola - 3. Ari - 4. Clo | 1. Ris - 2. Ola - 3. Que - 4. Clo |
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | - | £485,185 | £304,305 | Dominant |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | - | - | £131,559 | Dominant |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | - | - | - | Dominant |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | - | - | - | - |

**Figure 3: Cost effectiveness plane – dosing scenario 2**




## 8.3 Adverse event sensitivity analysis

Data on agitation were available for aripiprazole, risperidone and quetiapine. As no data were available for rates of aggression experienced by patients in the identified studies, a sensitivity analysis was carried out using agitation as a proxy. Therefore, in this analysis, the adverse events considered were weight gain, somnolence and EPS (akathisia and tremor represent symptoms of EPS) and agitation.

The results of this analysis are shown in Table 10 and Table 11. The overall direction of results does not change. The sequence with the highest QALYs is Aripiprazole - Risperidone - Olanzapine – Clozapine. The lowest cost sequence is Risperidone - Olanzapine - Aripiprazole – Clozapine. The cost effectiveness plane generated is shown in Figure 4.

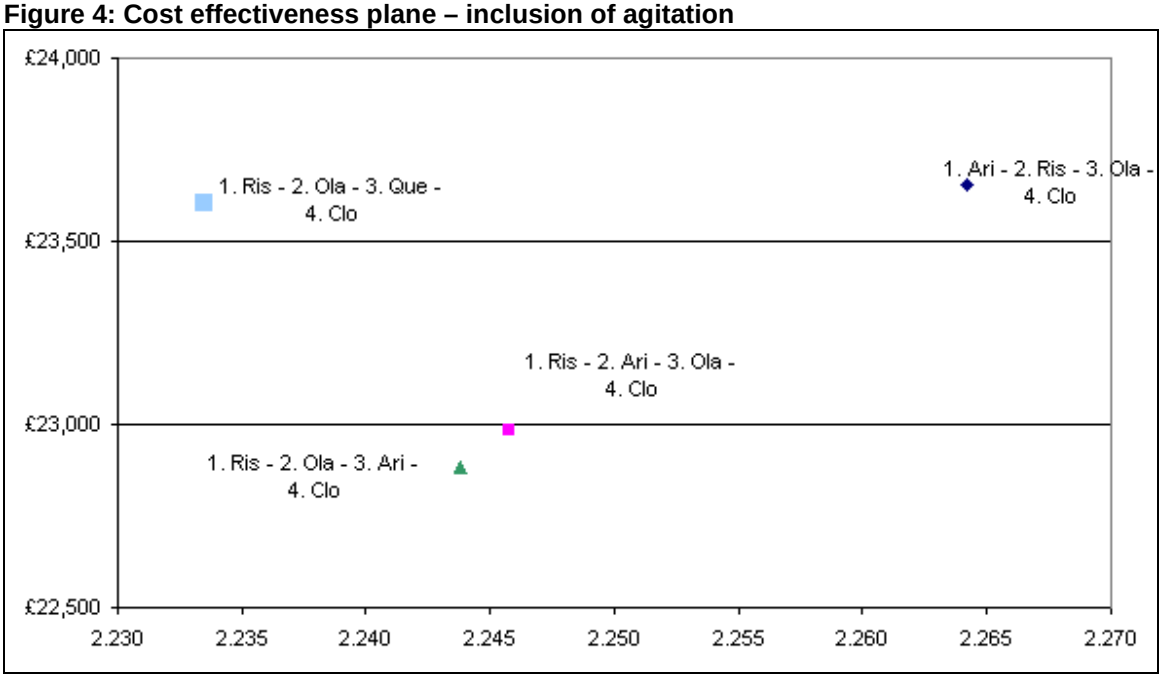
**Table 10: Total costs and total QALYs for dosing scenario 1**

| | Sequence | Total costs | Total QALYs |
|---|---|---|---|
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | £23,653 | 2.264 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | £22,982 | 2.246 |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | £22,884 | 2.244 |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | £23,607 | 2.233 |

**Table 11: ICERs for dosing scenario 1**

| | | A | B | C | D |
|---|---|---|---|---|---|
| | | 1. Ari - 2. Ris - 3. Ola - 4. Clo | 1. Ris - 2. Ari - 3. Ola - 4. Clo | 1. Ris - 2. Ola - 3. Ari - 4. Clo | 1. Ris - 2. Ola - 3. Que - 4. Clo |
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | - | £36,257 | £37,563 | £1,485 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | - | - | £49,893 | Dominant |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | - | - | - | Dominant |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | - | - | - | - |

**Figure 4: Cost effectiveness plane – inclusion of agitation**




## 8.4 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses were performed. The mean total costs and QALYs are shown in Table 12. The ICERs resulting from the PSA are shown in Table 13.

**Table 12: Total mean costs and QALYs from the PSA**

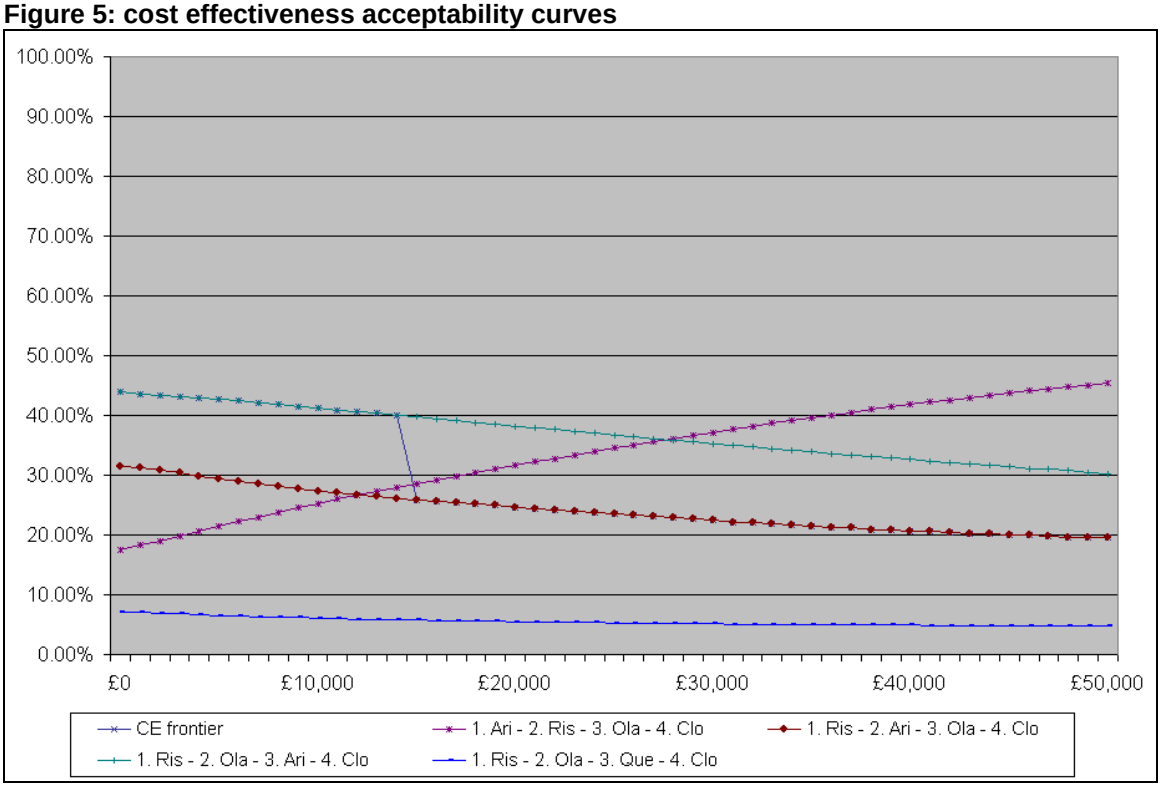
| | Sequence | Total costs | Total QALYs |
|---|---|---|---|
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | £23,212 | 2.355 |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | £22,579 | 2.343 |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | £22,533 | 2.339 |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | £23,510 | 2.327 |

**Table 13: ICERs resulting from the PSA**

| | | A | B | C | D |
|---|---|---|---|---|---|
| | | 1. Ari - 2. Ris - 3. Ola - 4. Clo | 1. Ris - 2. Ari - 3. Ola - 4. Clo | 1. Ris - 2. Ola - 3. Ari - 4. Clo | 1. Ris - 2. Ola - 3. Que - 4. Clo |
| **A** | 1. Ari - 2. Ris - 3. Ola - 4. Clo | - | £55,646 | £44,589 | Dominant |
| **B** | 1. Ris - 2. Ari - 3. Ola - 4. Clo | - | - | £11,817 | Dominant |
| **C** | 1. Ris - 2. Ola - 3. Ari - 4. Clo | - | - | - | Dominant |
| **D** | 1. Ris - 2. Ola - 3. Que - 4. Clo | - | - | - | - |

The cost effectiveness acceptability curves are shown in Figure 5.

**Figure 5: cost effectiveness acceptability curves**




- **Including aripiprazole in a four line treatment sequence is cost effective or dominant compared with four line treatment sequences that do not include aripiprazole in the treatment of adolescents with schizophrenia.**

- **In sensitivity analysis the overall direction of the results remains the same and in PSA, the cost effectiveness acceptability curves show how similar the treatment sequences are when compared with each other.**

## *9.Discussion*

The current analysis concludes that aripiprazole is a cost effectiveness treatment option for the treatment of schizophrenia in adolescents when compared with scenarios that do not include aripiprazole. Weaknesses of the model identified in the original submission remain in terms of lack of data, particularly for rates of relapse and utilities in the adolescent population. Given the lack of data for the adolescent population, comparison with previous analyses carried out with adult data has shown similar trends. For example, the NICE guideline model (NICE, 2009) ranked treatments in order of their potential cost effectiveness but concluded that extensive sensitivity analysis showed that results were characterised by high uncertainty and probabilistic analysis showed that no antipsychotic medication could be considered clearly cost-effective compared to the other options included in the assessment. The current model is also characterised by high levels of uncertainty in terms of input data.

Although the model was developed to reflect clinical practice as closely as possible, it was not designed to be a sequencing model. The aim of the model is not to evaluate a sequence of treatments but to investigate the impact of the first line antipsychotic on costs and patient outcomes and to accurately reflect clinical practice when patients discontinue treatment or have a relapse.

The results show a high level of uncertainty. This is most likely due to the very small differences in total costs and QALYs between the treatments, meaning that small changes in the model inputs can lead to large changes in the results. Relative risk of relapse remains one of the most influential parameters in the model. The potential for biasing against one specific treatment in this analysis is high and the results should be interpreted with caution.

## *References*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# *Appendix A*

## *Placebo controlled clinical trials overview*

| Study | Participants | Title | Drug, dose | Number randomised / completed | *Summary of Results* |
|---|---|---|---|---|---|
| **Aripiprazole** | | | | | |
| Findling 2008a | 302 adolescents aged 13–17 years with DSM-IV diagnosis of schizophrenia and PANSS total score ≥70 | A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia | Placebo<br>Aripiprazole 10 mg/day<br>Aripiprazole 30 mg/day | 108 / 98<br>115 / 99<br>115 / 97 | Of 302 patients, 85% completed the 6-week study. The mean baseline PANSS score was 94.1. At the end of the study, both aripiprazole doses showed statistically significant differences from placebo in reduction in PANSS total score. Adverse events occurring in more than 5% of either aripiprazole group and with a combined incidence at least twice the rate for placebo were extrapyramidal disorder, somnolence, and tremor. Mean changes in prolactin were –8.45, –11.93, and –15.14 ng/ml for placebo and 10 mg and 30 mg of aripiprazole, respectively. Mean body weight changes were –0.8, 0.0, and 0.2 kg for placebo and 10 mg and 30 mg of aripiprazole, respectively. |
| **Risperidone** | | | | | |
| Haas 2009a | 160 adolescents aged 13–17 years with acute exacerbation of schizophrenia and PANSS total score 60-120 | A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia | Placebo<br>Risperidone 1-3 mg/day<br>Risperidone 4-6 mg/day | 54 / 54<br>55 / 54<br>51 / 50 | Significant improvements occurred in both risperidone groups versus placebo ($p < 0.001$) in PANSS total change scores (placebo, -8.9 [16.1]; risperidone 1–3 mg, -21.3 [19.6]; risperidone 4–6 mg, -21.2 [18.3]) and clinical response rates (35%, 65%, 72%, respectively). Overall AE rates were more common in risperidone groups (75% and 76%) versus placebo (54%). Risperidone 4–6 mg/day had a higher incidence of extrapyramidal disorder, dizziness, and hypertonia than risperidone 1–3 mg. No prolactin-related AEs occurred. Overall EPS severity was low. |

| Study | Participants | Title | Drug, dose | Number randomised / completed | *Summary of Results* |
|---|---|---|---|---|---|
| **Olanzapine** | | | | | |
| Kryzhanovskaya 2009 | 107 inpatient and outpatient adolescents with DSM-IV schizophrenia and BPRS-C total score ≥35 | Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial | Placebo<br>Olanzapine 2.5-20 mg/day | 35 / 15<br>72 / 49 | More olanzapine-treated versus placebo-treated patients completed the trial (68.1% versus 42.9%, p =*0*.020). *O*lanzapine-treated adolescents had significantly greater improvement in Brief Psychiatric Rating Scale for Children total (p =*0*.003), Clinical Global Impressions Scale-Severity of Illness (p =*0*.004), PANSS total (p =*0*.005), and PANSS positive scores (p =*0*.002). Olanzapine-treated patients gained significantly more baseline-to-endpoint weight (4.3 kg versus 0.1 kg, p<*0*.001). Significantly more olanzapine-treated versus placebo-treated patients gained 7% or greater of their body weight at any time during treatment (45.8% versus 14.7%, p =*0*.002). Prolactin and triglyceride mean baseline-to-endpoint changes were significantly higher in olanzapine-treated versus placebo-treated adolescents. The incidence of treatment-emergent significant changes in fasting glucose, cholesterol, or triglycerides did not differ between the groups at endpoint, but significantly more olanzapine-treated patients had high triglycerides at any time during treatment. |
| **Quetiapine** | | | | | |
| Findling 2008b | 302 adolescents aged 13–17 years with DSM-IV diagnosis of schizophrenia and PANSS total score ≥60 | Efficacy and safety of quetiapine in adolescents with schizophrenia: a 6-week, double-blind, randomized, placebo-controlled trial | Placebo<br>Quetiapine 400 mg/day<br>Quetiapine 800 mg/day | 73 / 47<br>73 / 56<br>74 / 61 | Overall completion rates were 76.7% in quetiapine 400 mg/d, 82.4% in quetiapine 800 mg/d, and 62.7% in placebo group. LS mean change in PANSS total score at Day 42 was –27.31 for quetiapine 400 mg/d, –28.44 for quetiapine 800 mg/d, and –19.15 for placebo (P=0.043 and 0.009 for quetiapine 400 and 800 mg/d, respectively, versus placebo). Study withdrawal rates due to AEs were 6.9%, 9.5%, and 2.7% for quetiapine 400 mg/d, quetiapine 800 mg/d, and placebo, respectively. The most common AEs in the quetiapine groups included somnolence, insomnia, headache, and dizziness. Mean weight change at Day 42 was 2.2, 1.8, and –0.4 kg for the quetiapine 400 mg/d, quetiapine 800 mg/d, and placebo groups, respectively. |

## *Appendix B*

## *Summary of efficacy endpoints*

## Comparisons of PANSS Total Score

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Baseline | 95.0 | 15.5 | 93.7 | 15.7 | 94.9 | 15.5 | 0.54 | 0.94 |
| Change at Wk 6 | **-21.2** | **1.9** | **-26.7** | **1.9** | **-28.6** | **0.9** | **0.05** | **0.007** |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Baseline | - | - | - | - | - | - | - | - |
| Change at Wk 6 | **-10.3** | **-** | **-23.0** | **-** | **-23.7** | **-** | **<0.001** | **<0.001** |

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | 95.5 | 14.1 | 95.3 | 14.1 | 0.902 |
| Change at Wk 6 | **-8.8** | **-** | **-21.3** | **-** | **0.005** |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | 97.2 | 16.83 | 98.1 | 15.41 | 97.7 | 15.32 | - | - |
| Change at Wk 6 | **-19.15** | **3.04** | **-27.31** | **2.64** | **-28.44** | **1.82** | **0.043** | **0.009** |

Aripiprazole 30mg demonstrated a significant improvement in the PANSS Total score compared with placebo. Risperidone (1-3mg and 4-6mg) also showed a significant improvement in the PANSS Total score compared with placebo. No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population. Both Olanzapine (2.5-20mg) and quetiapine (400mg and 800mg) demonstrated a significant improvement in the PANSS Total score in this population.

## Comparisons of PANSS Positive Score

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Baseline | 22.9 | 5.6 | 22.1 | 5.0 | 23.5 | 5.0 | 0.26 | 0.47 |
| Change at Wk 6 | **-5.6** | **0.6** | **-7.6** | **0.6** | **-8.1** | **0.6** | **0.02** | **0.002** |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Baseline | 26.8 | 5.2 | 26.5 | 5.1 | 25.7 | 4.1 | - | - |
| Change at Wk 6 | **-3.0** | **6.3** | **-6.3** | **6.5** | **-6.5** | **5.4** | **<0.001** | **<0.001** |

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | 22.7 | | 22.8 | | |
| Change at Wk 6 | **-2.7** | | **-6.6** | | **0.002** |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | - | - | - | - | - | - | - | - |
| Change at Wk 6 | **-** | **-** | **-** | **-** | **-** | **-** | **0.075** | **0.008** |

Aripiprazole (10mg and 30mg) demonstrated a significant improvement in the PANSS positive score compared with placebo. Risperidone (1-3mg and 4-6mg) also showed a significant improvement in the PANSS positive measure compared with placebo. No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population. Olanzapine (2.5-20mg) and quetiapine (800mg) demonstrated a significant improvement in the PANSS positive score in this population.

## Comparisons of PANSS Negative Score

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Baseline | 25.6 | 6.0 | 25.4 | 6.8 | 24.9 | 6.2 | 0.79 | 0.40 |
| Change at Wk 6 | **-5.4** | **0.6** | **-6.9** | **0.6** | **-6.6** | **0.6** | **0.05** | **0.10** |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Baseline | 23.0 | 4.7 | 24.1 | 4.8 | 23.7 | 4.3 | - | - |
| Change at Wk 6 | **-1.9** | **4.3** | **-5.4** | **6.1** | **-4.9** | **4.9** | **<0.001** | **0.002** |

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | 24.8 | 6.2 | 24.9 | 5.6 | 0.969 |
| Change at Wk 6 | **-1.8** | **-** | **-3.8** | **-** | **0.081** |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | 24.8 | 5.85 | 25.4 | 5.65 | 25.8 | 5.43 | - | - |
| Change at Wk 6 | **-** | **-** | **-** | **-** | **-** | **-** | **ns** | **ns** |

Aripiprazole demonstrated no significant difference in the PANSS negative score compared with placebo. Risperidone (1-3mg and 4-6mg) were both able to show a significant improvement in the PANSS negative measure compared with placebo. No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population. Neither olanzapine (2.5-20mg) nor quetiapine (400mg and 800mg) had any significant effect on the PANSS negative score in this population.

## Comparisons of CGI-S

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Baseline | 4.6 | 0.8 | 4.5 | 0.8 | 4.6 | 0.6 | 0.24 | 0.60 |
| Change at Wk 6 | **-0.9** | **0.1** | **-1.2** | **0.1** | **-1.3** | **0.1** | **0.008** | **0.002** |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Baseline | 4.6 | 0.7 | 4.7 | 0.8 | 4.5 | 0.7 | - | - |
| Change at Wk 6* | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |

* CGI-S ratings indicated that subjects who received risperidone 1–3 mg or risperidone 4–6 mg had lower severity of illness at end point relative to subjects who received placebo (shown in barcharts, no values given).

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | 4.9 | - | 4.8 | - | - |
| Change at Wk 6 | **-0.5** | **-** | **-1.1** | **-** | **0.004** |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | 4.7 | 0.67 | 4.7 | 0.77 | 4.6 | 0.76 | - | |
| Change at Wk 6 | **-** | **-** | **-** | **-** | **-** | **-** | **0.104** | **0.018** |

Aripiprazole (10mg and 30mg) demonstrated a significant improvement in the CGI-Severity score compared with placebo at week 6. No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population. Olanzapine (2.5-20mg/kg/day) also showed a significant improvement in the CGI-Severity scale at week 6. Quetiapine 800mg/ day but not 400mg/ day demonstrated a significant improvement in the CGI-Severity scale at week 6.

## Comparisons of CGI-I

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Wk 1 | 3.8 | 0.1 | 3.6 | 0.1 | 3.4 | 0.1 | 0.02 | 0.002 |
| Wk 6 | 3.1 | 0.1 | 2.7 | 0.1 | 2.5 | 0.1 | 0.02 | 0.0004 |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Baseline | - | - | - | - | - | - | - | - |
| Change at Wk 6* | - | - | - | - | - | - | - | - |

* CGI-I ratings indicated that subjects who received risperidone 1–3 mg or risperidone 4–6 mg had greater improvement at end point relative to subjects who received placebo (shown in barcharts, no values given).

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | - | - | - | - | - |
| Endpoint | 3.8 | - | 2.7 | - | <0.001 |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | - | - | - | - | - | - | - | |
| Change at Wk 6 | - | - | - | - | - | - | 0.013 | <0.001 |

Aripiprazole 10mg and 30mg both demonstrated a significant benefit in the Clinical Global Impression-Improvement scale (CGI-I) compared with placebo. CGI-I ratings indicated that subjects who received risperidone 1–3 mg or 4–6 mg had greater improvement at end point relative to subjects who received placebo (no values given). No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population. Both olanzapine (2.5-20mg) and quetiapine (400mg and 800mg) demonstrated a significant improvement in the CGI-I score in this population.

## Comparisons of CGAS

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Baseline | 45.4 | 11.2 | 46.7 | 12.6 | 45.6 | 12.0 | 0.43 | 0.87 |
| Change at Wk 6 | **9.8** | **1.3** | **14.7** | **1.5** | **14.8** | **1.3** | **0.006** | **0.005** |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Screening | 42.2 | 12.3 | 39.0 | 12.7 | 41.9 | 11.6 | - | |
| Change at Wk 6 | **7.9** | **14.8** | **16.9** | **16.0** | **18.9** | **18.4** | **0.006** | **<0.001** |

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | - | - | - | - | - |
| Endpoint | **-** | **-** | **-** | **-** | **-** |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | - | - | - | - | - | - | - | |
| Change at Wk 6 | **-** | **-** | **-** | **-** | **-** | **-** | **0.139** | **0.019** |

Aripiprazole (10mg and 30mg) demonstrated a significant improvement in the Children's Global Assessment Scale compared with placebo. Risperidone (1-3mg and 4-6mg) also showed a significant improvement in the CGAS compared with placebo. No randomised placebo-controlled data are available for amisulpride, olanzapine or clozapine in the adolescent schizophrenia population. Quetiapine (800mg) demonstrated a significant improvement in the CGAS score.

## Comparisons of PQLES-Q

Findling et al 2008a

| | Placebo | | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Aripiprazole vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 10mg | 30mg |
| Baseline | 3.4 | 0.9 | 3.2 | 0.9 | 3.3 | 1.1 | 0.48 | 0.27 |
| Change at Wk 6 | **0.1** | **0.1** | **0.6** | **0.1** | **0.6** | **0.1** | **0.005** | **0.003** |

Haas et al 2009a

| | Placebo | | Risperidone 1-3mg/day | | Risperidone 4-6mg/day | | Risperidone vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 1-3mg/day | 4-6mg/day |
| Baseline | - | - | - | - | - | - | - | - |
| Change at Wk 6 | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |

Kryzhanovskaya et al 2009

| | Placebo | | Olanzapine 2.5-20mg/day | | Olanzapine vs placebo P values |
|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | 2.5-20mg/day |
| Baseline | - | - | - | - | - |
| Endpoint | **-** | **-** | **-** | **-** | **-** |

Findling et al 2008b

| | Placebo | | Quetiapine 400mg/day | | Quetiapine 800mg/day | | Quetiapine vs placebo P values | |
|---|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | 400mg/day | 800mg/day |
| Baseline | - | - | - | - | - | - | - | - |
| Change at Wk 6 | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |

On the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire Scale (PQLES-Q) both aripiprazole groups (10mg and 30mg) demonstrated a significant improvement compared with placebo. No randomised placebo-controlled data are available for risperidone, amisulpride, clozapine, olanzapine or quetiapine in the adolescent schizophrenia population.

## *Appendix C.*

## *Summary of safety endpoints*

## Comparisons of weight gain

Findling et al 2008a

| | Placebo | Aripiprazole 10 mg | Aripiprazole 30 mg | Aripiprazole vs placebo P values |
|---|---|---|---|---|
| Mean Change (Kg) | –0.8 | 0 | 0.2 | NS (10mg)<br>NS (30 mg) |

Haas et al 2009b

| | Placebo | Risperidone 0.5-2.5 mg/day | Risperidone 3-6mg/day | Risperidone vs placebo P values |
|---|---|---|---|---|
| Mean change (Kg) | 0.12 | 1.3 | 1.5 | - |

Kryzhanovskaya et al 2009

| | Placebo | Olanzapine 2.5-20mg/day | Olanzapine vs placebo P values |
|---|---|---|---|
| Mean change (Kg) | 0.1 | 4.3 | p<0.001 |

Findling et al 2008b

| | Placebo | Quetiapine 400mg/day | Quetiapine 800mg/day | Quetiapine vs placebo P values |
|---|---|---|---|---|
| Mean change (Kg) | –0.4 | 2.2 | 1.8 | - |
| Prop. with weight gain ≥7% | 6.8% | 23.2% | 18.2% | |

No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population.

## Comparisons of prolactin

Findling et al 2008a

| | Placebo | Aripiprazole 10 mg | Aripiprazole 30 mg | Aripiprazole vs placebo P values |
|---|---|---|---|---|
| Mean Change (ng/mL) | –8.5 | –11.9 | –15.1 | p<0.05(10 mg)<br>p<0.05 (30 mg) |

Haas et al 2009b

| | Placebo | Risperidone 0.5-2.5 mg/day | Risperidone 3-6mg/day | Risperidone vs placebo P values |
|---|---|---|---|---|
| Mean change (ng/mL) | -9.2 (females)<br>-3.2 (males) | +36.9 (females)<br>+16.0 (males) | +77.3 (females)<br>+26.4 (males) | - |

Kryzhanovskaya et al 2009

| | Placebo | Olanzapine 2.5-20mg/day | Olanzapine vs placebo P values |
|---|---|---|---|
| Mean change (ng/mL) | –3.3 | +8.8 | P=0.002 |

Findling et al 2008b

| | Placebo | Quetiapine 400mg/day | Quetiapine 800mg/day | Quetiapine vs placebo P values |
|---|---|---|---|---|
| Mean change (ng/mL) | –18.25 | –10.55 | –7.83 | - |

No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population.

## Comparisons of incidence of akathisia

Findling et al 2008a

| | Placebo | Aripiprazole 10 mg | Aripiprazole 30 mg | Aripiprazole vs placebo P values |
|---|---|---|---|---|
| % with symptoms | 5 | 5 | 12 | NS(10mg)<br>NS (30 mg) |

Haas et al 2009b

| | Placebo | Risperidone 0.5-2.5 mg/day | Risperidone 3-6mg/day | Risperidone vs placebo P values |
|---|---|---|---|---|
| Prop with Global Clinical rating of Akathisia = 0 (%) | Baseline : 96 | 96 | 90 | - |
| | Endpoint : 96 | 91 | 90 | |

Kryzhanovskaya et al 2009

| | Placebo | Olanzapine 2.5-20mg/day | Olanzapine vs placebo P values |
|---|---|---|---|
| Barnes Akathisia Scale global assessment | - | - | 0.747 |

Findling et al 2008b

| | Placebo | Quetiapine 400mg/day | Quetiapine 800mg/day | Quetiapine vs placebo P values |
|---|---|---|---|---|
| % with symptoms | 2.7 | 4.1 | 4.1 | - |

No randomised placebo-controlled data are available for amisulpride or clozapine in the adolescent schizophrenia population.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

## *Appendix D*

## *Health Economics*

## Data used in the analyses

A summary of the data used from Findling et al (2008) (aripiprazole trial) and Study 31-03-239 (aripiprazole) and Kryzhanovskaya et al (2009) for olanzapine are provided in Table 14 and Table 15. As in the original submission (section 5.7), for patients receiving benzodiazepines, the CSR for aripiprazole lists the psycholeptic treatments that patients received during the trial. From this list, the number of patients receiving treatments classed as benzodiazepines were extracted and used in the indirect comparison to provide a proxy for extrapyramidal symptoms which could be compared with olanzapine in sensitivity analyses.

Additional data to inform the economic model were extracted from Haas et al. 2009 and Findling et al. 2008 on risperidone and quetiapine respectively. The identification of these data sources allows additional indirect comparisons for aripiprazole versus risperidone and quetiapine for akathisia, tremor and agitation. The data from these sources is outlined in the tables below.

**Table 14: Data used in the analyses for aripiprazole (10mgs)**

| | **Aripiprazole (10mg) (N=100*)** | **Placebo (N=100*)** |
|---|---|---|
| | Number of patients with event n (%) | Number of patients with event n (%) |
| Withdrawals due to adverse events | 7 (7%) | 2 (2%) |
| Withdrawals due to lack of efficacy | [redacted] | [redacted] |
| Withdrawals due to other reasons | [redacted] | [redacted] |
| Significant weight increase from baseline of ≥ 7%* | [redacted] | [redacted] |
| Somnolence | 11 (11%) | 6 (6%) |
| Akathisia | 5 (5%) | 5 (5%) |
| Tremor | 2 (2%) | 2 (%) |
| Participants received benzodiazepines | [redacted] | [redacted] |
| Agitation | 1 (1%) | 5 (5%) |

* aripiprazole N=84, placebo N = 89, underline and highlighted in red = CIC

**Table 15: Data used in the analyses for olanzapine (flexible dosing)**

| | Olanzapine (flexible dosing) (N=72) | Placebo (N=35) |
|---|---|---|
| | Number of patients with event n (%) | Number of patients with event n (%) |
| Withdrawals due to adverse events | 5 (7%) | 0 (0%) |
| Withdrawals due to lack of efficacy | 10 (14%) | 18 (51%) |
| Withdrawals due to other reasons | 8 (11%) | 2 (6%) |
| Significant weight increase from baseline of ≥ 7% | 33 (46%) | 5 (14%) |
| Somnolence | 17 (24%) | 1 (3%) |
| Akathisia | NR | NR |
| Tremor | NR | NR |
| Participants received benzodiazepines | 21 (29%) | 18 (51%) |
| Agitation | NR | NR |

NR – values not reported (additional data on these outcomes were not available)

**Table 16: Data used in the analyses for risperidone (1-3mgs and 4-6mgs))**

| | Risperidone 1-3mg (N=55) | Risperidone 4-6mg (N=51) | Placebo (N=54) |
|---|---|---|---|
| | Number of patients with event n (%) | Number of patients with event n (%) | Number of patients with event n (%) |
| Withdrawals due to adverse events | 3 (5%) | 4 (8%) | 2 (4%) |
| Withdrawals due to lack of efficacy | 3 (5%) | 1 (2%) | 13 (24%) |
| Withdrawals due to other reasons | 4 (7%) | 2 (4%) | 3 (6%) |
| Significant weight increase from baseline of ≥ 7% | NR | NR | NR |
| Somnolence | 13 (24%) | 6 (11%) | 2 (4%) |
| Akathisia | NR | NR | NR |
| Tremor | 6 (11%) | 5 (10%) | 3 (6%) |
| Participants received benzodiazepines | NR | NR | NR |
| Agitation | 8 (15%) | 4 (8%) | 4 (7%) |

NR – values not reported

**Table 17: Data used in the analyses for quetiapine (400mgs and 800mgs)**

| | Quetiapine 400mg (N=73) | Quetiapine 800mg (N=74) | Placebo (N=75)* |
|---|---|---|---|
| | Number of patients with event n (%) | Number of patients with event n (%) | Number of patients with event n (%) |
| Withdrawals due to adverse events | 5 (7%) | 7 (9%) | 2 (3%) |
| Withdrawals due to lack of efficacy** | NA | NA | NA |
| Withdrawals due to other reasons | 12 (16%) | 6 (8%) | 26 (35%) |
| Significant weight increase from baseline of ≥ 7% | 17 (23%) | 13 (18%) | 5 (7%) |
| Somnolence | 20 (27%) | 22 (30%) | 25 (33%) |
| Akathisia | 3 (4%) | 3 (4%) | 2 (3%) |
| Tremor | 3 (4%) | 3 (4%) | 2 (3%) |
| Participants received benzodiazepines | 18 (25%) | 13 (18%) | 19 (25%) |
| Agitation | 6 (8%) | 6 (8%) | 10 (13%) |

NA – not available

* Note that the Findling et al 2008 abstract stated that the safety and ITT populations comprised 222 and 220 patients, respectively. All data on outcomes required for the model appeared to be based on the safety population and therefore this has been reported above.

**withdrawals due to lack of efficacy have not been included here separately to avoid double counting as they are assumed to be contained within the 'withdrawals due to other reasons' group.

An indirect comparison using methods for dichotomous data was carried out to compare aripiprazole with olanzapine, risperidone and quetiapine. The indirect comparison methods used are described in section 5.7 of the original submission. The odds ratios produced from this indirect comparison are provided in Table 3 of section 6.1 of this report.